# PATENT COOPERATION TREATY

# PCT



# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference P104185WO | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No. PCT/GB2004/003899 | International filing date *(day/month/year)* 13.09.2004 | Priority date *(day/month/year)* 04.12.2003 |
| International Patent Classification (IPC) or national classification and IPC G01N33/574, C07K16/00, A61K38/16 | | |
| Applicant LUDWIG INSTITUTE FOR CANCER RESEARCH et al. | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1-8 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 11.05.2005 | 19.01.2006 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Thumb, W Telephone No. +49 89 2399-7350 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/003899

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

| | |
|---|---|
| **Description, Pages** | |
| 1-45 | as originally filed |
| **Sequence listings part of the description, Pages** | |
| 1-30 | received on 30.12.2004 with letter of 23.12.2004 |
| **Claims, Numbers** | |
| 1-44 | filed with telefax on 07.06.2005 |
| **Drawings, Sheets** | |
| 1/39-39/39 | as originally filed |

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 25,27-33
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/003899

## Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 36,37

because:

☒ the said international application, or the said claims Nos. 36,37 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | | |
|---|---|---|
| the written form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |
| the computer readable form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/003899

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-24,26,27,29-44 |
| | No: | Claims | 25,28 |
| Inventive step (IS) | Yes: | Claims | 1-24,26,38-44 |
| | No: | Claims | 25,27-37 |
| Industrial applicability (IA) | Yes: | Claims | 1-35,38-44 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

## Supplemental Box relating to Sequence Listing

**Continuation of Box I, item 2:**

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

**Re Item I**

**Basis of the report**

1. Claims 25 and 27 have been amended to read "*A transfected cell wherein the genome of said cell is modified to* ***consist*** *of at least one copy of .....*" (emphasis added). In the broadest interpretation of the wording of said claims they refer to cells having a genome consisting only of two nucleic acid molecules defined by sequences 17a or 17b and 18a, 18c, 18e, 18g, or 21a, respectively.
Such cells are not disclosed in the specification as originally filed. Claims 25 and 27 thus contravene the provisions of Article 34(2)(b) PCT.
Theses amendments will thus not be taken into consideration in the following opinion on novelty and inventive step of claims 25, and 27-33.

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 36 and 37 pertain to a method of treatment of the human or animal body which are covered by the provisions of Rule 67.1(iv) PCT.
Consequently, no opinion will be formulated with respect of the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Novelty

1.1 The document BERGAMASCHI D ET AL: "IASPP ONCOPROTEIN IS A KEY INHIBITOR OF P53 CONSERVED FROM WORM TO HUMAN" NATURE GENETICS, NATURE AMERICA, NEW YORK, US, vol. 33, no. 2, February 2003 (2003-02), pages 162-167 (D3) discloses cotransformation of cells with *ras* and

ASPP1 or ASPP2 (see in particular figure 4c).
D3 is thus novelty-destroying of the subject-matter of claims 25 and 28 (Article 33(2) PCT).

1.2 The other claims meet the requirements of Article 33(2) PCT.

2. Inventive step

2.1 Claim 1 meets the requirements of Articles 33(3) PCT, the reasons being as follows:

Documents D3 and D4 (IWABUCHI KUNIYOSHI ET AL: "Stimulation of p53-mediated transcriptional activation by the p53-binding proteins, 53BP1 and 53BP2" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 273, no. 40, 2 October 1998 (1998-10-02), pages 26061-26068, XP002189291 ISSN: 0021-9258), which both could be considered as representing the most relevant state of the art, indicate that members of the ASPP protein family have an influence on the transforming activity of ras (D3: page 164, col. 1, paragraph 4; D4: page 26066, col. 1, paragraph 2 and table 1).
The subject-matter of claim 1 differs from the teaching of D3 or D4 in that the interaction of ASPP1 or ASPP2 (represented by the sequences shown in Figures 17a or 17b) with different forms of *ras* is used in a screening assay to identify compounds having an effect on this interaction.
Documents D3 and D4 only describe an effect of ASPP proteins on the transforming activity of *ras* without further discussing the underlying biological mechanism.
Therefore, D3 and D4 do not indicate that members of the *ras* family and of the ASPP protein family actually interact with each other. To the contrary, in D4 it is speculated that this effect may be achieved through the tumor suppressor function of p53, via interaction of 53BP2 with p53.
Therefore, based on the teaching of D3 or D4, or any other document cited in the international search report, it would not be obvious to use a *ras*-ASPP interaction assay in order to identify compounds having an influence on said interaction.
Claims 1-15 thus meet the requirements of Articles 33(2) and (3) PCT.

2.2 Claims 16 and 17 also meet the requirements of Articles 33(3) PCT.
Claims 16 and 17 pertain to the use kinases and phosphatases (i.e. MAP kinase, PKA, and Protein Phosphatase 1) in screening assays for identifying compounds which affect the phosphorylation state of ASPP1 or ASPP2.
The available prior art documents do not address the question of regulation of ASPP protein function by phosphorylation, let alone identify MAP kinase, PKA, or Protein Phosphatase 1 as being involved in said regulation.
Even though a number of signalling pathways regulating oncoprotein signalling are known in the state of the art (see for example LAIRD A D ET AL: "Oncoprotein signalling and mitosis" CELLULAR SIGNALLING, ELSEVIER SCIENCE LTD, GB, vol. 9, no. 3-4, 1997, pages 249-255, XP002301400 ISSN: 0898-6568 (D6), Figure 1) phosphorylation of ASPP protein family members is not described in the available state of the art.
It would therefore not be obvious to provide an assay based on detection of changes in the phosphorylation state of ASPP1 or ASPP2 caused by MAP kinase, PKA, or Protein Phosphatase 1.
Claims 16, 17 as well as the dependent claims 18-24 thus meet the requirements of Articles 33(3) PCT.

2.3 Claims 26 and 38-44 also meet the requirements of Articles 33(2) and (3) PCT following the argumentation put forward in the preceding paragraph.
Even though a number of antibodies (monoclonal and polyclonal antibodies, see for example document D2) directed against ASPP protein family members are described in the state of the art, antibodies binding to phosphorylated epitopes of ASPP proteins are not rendered obvious in the state of the art.

2.4 Claim 27 lacks an inventive step within the meaning of Article 33(3) PCT.
The document HELPS N R ET AL: "Protein Phosphatase 1 interacts with p53BP2, a protein which binds to tumor suppressor p53" FEBS LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 377, no. 3, 27 December 1995 (1995-12-27), pages 295-300, XP002095580 ISSN: 0014-5793 (D5) pertains to the interaction of protein phosphatase 1 with p53BP2.
The subject-matter of claim 27 differs from the teaching of D5 in that it refers to ASPP1 or ASPP2 coexpressed with Protein Phosphatase 1 (PP1)

The underlying objective technical problem may therefore be seen in providing a cell with a different interaction partner for PP1.
It is well known in the art that p53BP2 corresponds to a C-terminal fragment of ASPP2 (see document D3, abstract). Transfection of a cell with ASPP2 is also described in D3. It would therefore be obvious for a person skilled in the art to use ASPP2 in a cell for studying the interaction of PP1 with a member of the ASPP family of proteins in order to solve the above-stated problem.
Claim 27 thus lacks an inventive step within the meaning of Article 33(3) PCT.

2.5 Claims 29 and 30-33 cannot be considered as being inventive within the meaning of Article 33(3) PCT.
The putative role of p53 and ASPP and the influence of further regulatory factors in the development of cancer is discussed in the prior art (see for example document D3, abstract, D4, abstract and Introduction).
Using transgenic non-human animals for studying cellular function has become general background knowledge in the art.

2.6 Claim 34 does not meet the requirements of Article 33(3) PCT.
The claim refers to a preparation containing a nucleic acid encoding ASPP1 or ASPP2 together with p53 by a single molecule, and said nucleic acid molecules being operable linked to at least one promoter.
The document SAMUELS-LEV YARDENA ET AL: "ASPP proteins specifically stimulate the apoptotic function of p53" MOLECULAR CELL, CELL PRESS, CAMBRIDGE, MA, US, vol. 8, no. 4, October 2001 (2001-10), pages 781-794, XP002202189 ISSN: 1097-2765 (D1) discloses that members of the ASPP protein family enhance apoptotic function of p53. ASPP2 co-transfected with p53 (i.e. resulting in a composition comprising ASPP2 and p53) significantly enhances the transactivation function of p53 on a Bax-promoter in a p53-dependent manner (page 783, col. 2, paragraph 3 - page 784, col. 1, paragraph 1; see also the passages cited in the International Search Report).
On pages 791 and 792, implications of the ASPP2/p53 interaction in the development of cancer is discussed.
A possible role of stimulating the activity of ASPP family members in vivo for treating some human cancers is discussed (page 792. col. 2, paragraph 1).

The subject-matter of claim 34 differs from the teaching of document D1 in that it refers to a preparation and in that p53 and ASPP are encoded by a single nucleic acid molecule.

The objective underlying technical problem may therefore be seen in providing an alternative preparation for co-expression of p53 and ASPP.

Using apoptosis stimulating proteins in pharmaceutical preparations is disclosed in document D2 (e.g. page 48, line 23 et seq.), which also refers to the stimulation of p53 pro-apoptotic activity by ASPP family members (ASP2 of D2 comprises a region which is 100% identical to the protein defined by the sequence of Figure 17d of the present application).

Expressing two polypeptides from one nucleic acid vector instead of using two plasmids is a routine procedure in the art and is not suitable for providing an inventive step vis-à-vis the state of the art. Moreover, using a single nucleic acid does not appear to be associated with a surprising technical effect.

Given the clear implication of ASPP function in the regulation of p53 function, derived from co-expression experiments in D1, together with the teaching of document D2 it would be obvious for a person skilled in the art to combine nucleic acids encoding p53 and ASPP in a single molecule of a preparation in order to arrive at a solution to the above-stated problem.

It should also be noted that the teaching of the present application does not go beyond the disclosure of cellular in-vitro assays demonstrating the effect of ASPP on p53 activity. This is comparable to the disclosure of document D1. Thus the argument that D1 does not indicate a possible use of said substances in gene therapy cannot be accepted, since a) D1 already contemplates the use of ASPP proteins in the treatment of cancer, and b) the application does also not demonstrate the actual use of p53/ASPP co-expression in an in-vivo model.

Claims 34-37 thus do not meet the requirements of Article 33(3) PCT.

**Claims**

1. A screening method for the identification of agents which modulate, either directly or indirectly, the interaction of a first polypeptide encoded by a nucleic acid molecule selected from the group consisting of:

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 17a or 17b;

b) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (a) and which enhances the pro-apoptotic activity of p53;

c) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (a) and (b); with a second polypeptide selected from the group consisting of:

d) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 18a, 18c, 18e or 18g;

e) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (d) above and which has the activity associated with Ras or a variant Ras polypeptide;

f) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (d) and (e); comprising,

i) forming a preparation comprising said first and second polypeptide;

ii) adding at least one candidate agent to be tested; and

iii) determining the effect, or not, of said agent on the interaction of said first polypeptide with said second polypeptide.

2. A method according to Claim 1 wherein said first polypeptide is represented by the amino acid sequence as shown in Figure 17c or 17d, or a variant polypeptide wherein said variant polypeptide sequence has been altered by addition, substitution or deletion of at least one amino acid residue.

3. A method according to Claim 1 or 2 wherein said first polypeptide comprises the amino acid sequence + 1 to +120 of the sequence shown in Fig 17c and 17d .

4. A method according to Claim 3 wherein said polypeptide consists of the amino acid sequence +1 to +120 of the sequence shown in Figure 17c or 17d.

5. A method according to any of Claims 1-4 wherein said second polypeptide is represented by the amino acid sequence shown in Figure 18b, 18d, 18f or 18h, or a variant polypeptide wherein said variant polypeptide sequence has been altered by addition, substitution or deletion of at least one amino acid residue.

6 A method according to Claim 5 wherein said second polypeptide comprises the amino acid sequence as shown in Figure 18d.

7. A method according to Claim 5 or 6 wherein said second polypeptide comprises the amino acid sequence as shown in Figure 18h.

8. A method according to any of Claims 1-4 wherein said second polypeptide is modified at amino acid residue 17.

9. A method according to Claim 8 wherein said modification is the substitution of a serine amino acid for an asparagine amino acid.

10. A method according to any of Claims 1-9 wherein said first and second polypeptides are expressed by a cell.

11. A method according to Claim 10 wherein said cell is a cell transfected with at least one nucleic acid molecule(s) which encodes said first and second polypeptides.

12. A method according to Claim 10 or 11 wherein the expression of said nucleic acid molecule(s) is regulatable.

13. A method according to any of Claims 10-12 wherein said cell is a cancer cell.

14. A method according to any of Claims 10-13 wherein said cell is part of a transgenic animal wherein the genome of said animal has been modified to include nucleic acid molecules which encode first and second polypeptides.

15. A method according to any of Claims 10-14 wherein said nucleic acid molecules are expressed in a specific cell/tissue.

16. A screening method for the identification of agents which modulate, either directly or indirectly, the phosphorylation of a first polypeptide encoded by a nucleic acid molecule selected from the group consisting of:

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 17a or 17b;

b) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (a) and which enhances the pro-apoptotic activity of p53;

c) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (a) and (b); with a second polypeptide selected from the group consisting of:

d) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 19a or 20a;

e) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (d) above and which has protein kinase activity;

f) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (d) and (e); comprising,

i) forming a preparation comprising said first and second polypeptide;

ii) adding at least one candidate agent to be tested; and

iii) determining the effect, or not, of said agent on the phosphorylation state of said first polypeptide.

17. A screening method for the identification of agents which modulate, either directly or indirectly, the phosphorylation state of a first polypeptide encoded by a nucleic acid molecule selected from the group consisting of:

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 17a or 17b;

b) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (a) and which enhances the pro-apoptotic activity of p53;

c) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (a) and (b); with a second polypeptide selected from the group consisting of:

d) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 21a;

e) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (d) above and which has protein phosphatase activity;

f) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (d) and (e); comprising,

i) forming a preparation comprising said first and second polypeptide;

ii) adding at least one candidate agent to be tested; and

iii) determining the effect, or not, of said agent on the phosphorylation state of said first polypeptide.

18. A method according to any of Claims 1-17 wherein said agent is a polypeptide.

19. A method according to Claim 18 wherein said polypeptide is an antibody, or active binding fragment thereof.

20. A method according to Claim 19 wherein said antibody or binding fragment is a monoclonal antibody.

21. A method according to Claim 19 or 20 wherein said antibody fragment is a single chain antibody variable region fragment or a domain antibody fragment.

22. A method according to Claim 19 or 20 wherein said antibody is a humanised or chimeric antibody.

23. A method according to any of Claims 1-17 wherein said agent is a peptide.

24. A method according to any of Claims 1-17 wherein said agent is an aptamer.

25. A transfected cell wherein the genome of said cell is modified to consist of least one copy of a nucleic acid molecule encoding a polypeptide comprising a nucleic acid a sequence as represented in Figure 17a or 17b; and at least one copy of a nucleic acid molecule encoding a polypeptide selected from the group consisting of:

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 18a, 18c, 18e or 18g;

b) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (d) above and which has the activity associated with Ras or a variant Ras polypeptide;

c) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (a) and (b) wherein said cell is adapted for the regulated expression of said nucleic acid molecule(s).

26. A cell transfected with at least one nucleic acid molecule wherein the genome of said cell is modified to include at least one copy of a nucleic acid molecule encoding a polypeptide selected from the group consisting of:

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 17a or 17b;

b) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (a) and which enhances the pro-apoptotic activity of p53;

c) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (a) and (b) and at least one copy of a nucleic acid molecule encoding a polypeptide selected from the group consisting of;

d) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 19a or 20a;

e) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (d) above and which has protein kinase activity;

f) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (d) and (e) wherein said cell is adapted for the regulated expression of said nucleic acid molecule(s).

27. A transfected cell wherein the genome of said cell is modified to consist of at least one copy of a nucleic acid molecule encoding a polypeptide comprising a nucleic acid sequence as represented in Figure 17a or 17b; and at least one copy of a nucleic acid molecule encoding a polypeptide selected from the group consisting of;

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 21a;

b) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (d) above and which has protein phosphatase activity;

c) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (a) and (b) wherein said cell is adapted for the regulated expression of said nucleic acid molecule(s).

28. A cell according to any of Claims 25-27 wherein said cell further comprises a nucleic acid molecule which includes a reporter gene to monitor the activity of said pro-apoptotic polypeptide(s).

29. A cell according to any of Claims 25-28 wherein said cell is a cancer cell.

30. A non-human transgenic animal comprising at least one cell according to any of Claims 25-29.

31. An animal according to Claim 30 wherein said non-human animal is a non-human primate.

32. An animal according to Claim 30 wherein said transgenic animal is a rodent.

33. An animal according to Claim 30 wherein said transgenic animal is a pig.

34. A preparation comprising a nucleic acid molecule which encodes a p53 polypeptide, or sequence variant thereof, and at least one nucleic acid molecule which encodes at least one polypeptide, or sequence variant thereof, as represented by the amino acid sequences shown in Figure 17c and/or Figure 17d, wherein said polypeptides are encoded by a single nucleic acid molecule which is part of a vector and said nucleic acid molecules are operably linked to at least one promoter that controls the expression of said nucleic acid molecules.

35. A preparation according to Claim 34 for use as a pharmaceutical.

36. A method to treat a condition which would benefit from a stimulation of apoptosis comprising administering a combined preparation according to Claim 35.

37. A method according to Claim 36 wherein said condition is cancer.

38. An antibody, or active binding fragment thereof, wherein said antibody or fragment, specifically binds a polypeptide encoded by a nucleic acid molecule selected from the group consisting of:

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 17a or 17b;

b) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (a) and which enhances the pro-apoptotic activity of p53;

c) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (a) and (b), wherein said antibody binds a phosphorylated epitope.

39. An antibody according to Claim 38 wherein said antibody is a monoclonal antibody.

40. An antibody according to Claim 38 or 39 wherein said antibody fragment is a single chain antibody fragment or a domain antibody.

41. An antibody according to any of Claims 38-40 wherein said phosphorylated epitope comprises amino acid residue 671 of the amino acid sequence as shown in Figure 17c.

42. An antibody according to any of Claims 38-40 wherein said phosphorylated epitope comprises amino acid residue 698 of the amino acid sequence shown in Figure 17d.

43. An antibody according to any of Claims 38-40 wherein said phosphorylated epitope comprises amino acid residue 746 of the amino acid sequence as shown in Figure 17c.

44. An antibody according to any of Claims 38-40 wherein said phosphorylated epitope comprises amino acid residue 827 of the amino acid sequence shown in Figure 17d.